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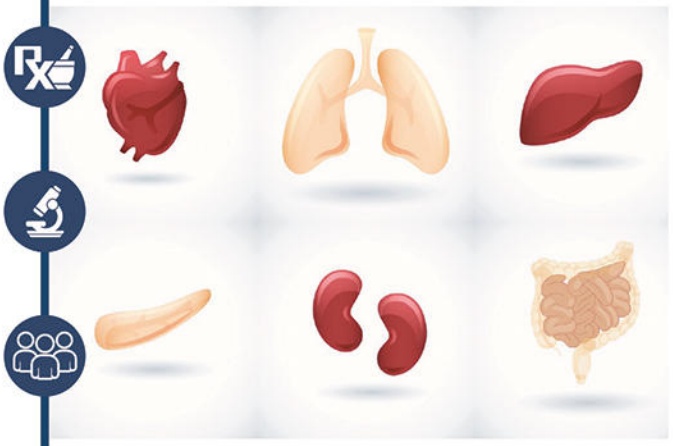

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ORIGINAL ARTICLE



# Dietary Approach to Stop Hypertension (DASH) diet and risk of renal function decline and all-cause mortality in renal transplant recipients

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Renal transplant recipients (RTR) are at risk of decline of graft function and premature mortality, with high blood pressure as an important risk factor for both. To study the association of the Dietary Approach to Stop Hypertension (DASH) diet with these adverse events, we conducted a prospective cohort study of adult RTR. Dietary data were collected using a validated 177-item food frequency questionnaire and an overall DASH-score was obtained. We included 632 stable RTR (mean ± standard deviation age 53.0 ± 12.7 years, 57% men). Mean DASH score was 23.8 ± 4.7. During median follow-up of 5.3 (interquartile range, 4.1-6.0) years, 119 (18.8%) RTR had renal function decline, defined as a combined endpoint of doubling of serum creatinine and death-censored graft failure, and 128 (20.3%) died. In Cox-regression analyses, RTR in the highest tertile of the DASH score had lower risk of both renal function decline (hazard ratio [HR] = 0.57; 95% confidence interval [CI], 0.33-0.96, $P$ = .03) and all-cause mortality (HR = 0.52; 95%CI, 0.32-0.83, $P$ = .006) compared to the lowest tertile, independent of potential confounders. Adherence to a DASH-style diet is associated with lower risk of both renal function decline and all-cause mortality. These results suggest that a healthful diet might benefit long-term outcome in RTR.

**KEYWORDS**
clinical research/practice, graft survival, kidney transplantation/nephrology, nutrition, patient survival

## 1 | INTRODUCTION

Currently, renal transplantation is the treatment of choice in patients with end-stage renal disease. Compared to dialysis, renal transplantation improves quality of life and survival, against lower medical costs.[1,2] The number of kidneys available for transplantation is limited and there is a growing discrepancy between supply and demand in organ transplantation.[3] Therefore, it is of major importance to optimize graft survival. Furthermore, patient survival of renal transplant recipients (RTR) is significantly lower compared to

**Abbreviations:** BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein (CRP); DASH, Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; FFQ, food frequency questionnaire; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RTR, renal transplant recipients; SBP, systolic blood pressure.

**Clinical Trial Registry number and website:** The cohort on which the study was based is registered at clinicaltrials.gov as "TransplantLines Food and Nutrition Biobank and Cohort Study (TxL-FN)" with number NCT02811835.

the general population.[4] In spite of previous developments, in the past 2 decades, there was only little improvement in long-term graft and patient survival after renal transplantation.[5] Approximately 50% of all renal allografts from deceased donors are lost in a period of 10-12 years after transplantation.[6] As a result of this stagnation, there is a growing interest in other factors that may influence graft and patient survival after renal transplantation, such as diet and other lifestyle factors.

Previous studies on diet often focused on single nutrients, but currently there is a growing interest in dietary patterns, since they can take into account complex interactions and are easier to interpret. Dietary patterns can directly be translated into dietary recommendations to be used in clinical practice.[7,8] Previously, we found that a Mediterranean-style diet is associated with a lower risk of new-onset diabetes and all-cause mortality after renal transplantation.[9] In contrast to the Mediterranean diet, which is based on a diet traditionally consumed by the inhabitants of regions surrounding the Mediterranean sea, the Dietary Approaches to Stop Hypertension (DASH) diet features a high intake of fruits, vegetables, whole grains (complex carbohydrates), low-fat dairy products, legumes and nuts, and a low intake of sodium, sweetened beverages, and red processed meat.[10,11]

Originally, the DASH diet was developed to reduce blood pressure, and considering that hypertension is associated with graft failure[12-14] and mortality in RTR,[15] the DASH diet might greatly benefit RTR. Yet, it has never been investigated whether the DASH diet is associated with graft and patient survival after renal transplantation. We hypothesized that the DASH diet is associated with a lower risk of renal function decline and all-cause mortality.

## 2 | SUBJECTS AND METHODS

### 2.1 | Study population

This observational prospective cohort study was conducted in a large single-center prospective cohort of RTR.[16,17] Adult RTR (≥18 years) with a functioning graft for at least 1 year and no history of alcohol and/or drug addiction were included. Furthermore, at inclusion, RTR in this study had no known or apparent systemic diseases, such as malignancies or active infections. Between November 2008 and May 2011, patients who visited the outpatient clinic of the University Medical Center Groningen (UMCG) were invited to participate. Of the initial 817 invited patients, 707 (86.5%) signed written informed consent. The study was observational in nature and no study based protocols were applied to monitor the adherence of patients to healthy dietary lifestyles. As part of our routine, patients receive 1 consult of a dietitian, who provides advice about a healthy diet, with special attention to sodium restriction. For our study, we excluded patients with missing dietary data (n = 75), leaving 632 RTR eligible for analyses (Supplemental Figure S1). The institutional review board approved this research project (METc 2008/186), and it is in adherence to the guidelines of the Declaration of Helsinki.

### 2.2 | Data collection

All baseline measurements were performed once at baseline during a morning visit to the outpatient clinic as described previously.[18] Body weight and height were measured, and body mass index (BMI) was calculated as weight divided by height squared (kg/m$^2$). A semi-automatic device (Dinamap®1846; Critikon, Tampa, FL) was used to measure blood pressure and heart rate every minute for 15 minutes in a half-sitting position. The average of the last 3 measurements was taken as the blood pressure value. Information on medication was derived from patient records, whereas information on smoking behavior was obtained by a questionnaire. Information on physical activity was obtained using the reliable and valid Short Questionnaire to Assess Health enhancing physical activity score in time multiplied by intensity.[19] Blood was drawn after an 8-12-hour overnight fasting period in the morning after completion of 24-hour urine collection. RTR were instructed to assure adequate urine collection. They were instructed to discard their first morning urine specimen and then collect their urine for the next 24 hours, including the next morning's first specimen of the day of their visit. The serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation[20] was used to calculate the estimated glomerular filtration rate (eGFR).

### 2.3 | Dietary intake assessment

A semiquantitative food frequency questionnaire (FFQ) was used to obtain information on dietary intake during the last month, taking into account seasonal variations. The FFQ was developed at Wageningen University, consisted of 177 items, was reproducible, biomarker validated,[21,22] and updated several times. The frequency of each of the food items was recorded in times per day, week, or month. Expression of number of servings was in either natural units, such as a slice of bread or an apple, or in household measures, for example, a cup or a teaspoon. Subsequently, all dietary data were converted into total energy and nutrient intake per day using the Dutch Food Composition Table (NEVO 2006). The FFQ was validated by comparing the protein intake of the FFQ with the protein intake calculated by the Maroni Equation, using urinary urea excretion values.[17]

### 2.4 | DASH score

The DASH score was constructed as previously described[10,11] and is based on 8 recommendations: high intake of fruits, vegetables, legumes and nuts, whole grains, low-fat dairy products and low intake of sodium, red and processed meats, and sugar-sweetened beverages (Supplemental Table S1). Sodium intake was determined based on 24-hour urinary sodium excretion, which is considered the criterion standard to assess daily sodium intake.[23] For each of the components, subjects were classified into sex-specific quintiles according to their intake. For each of the components (fruit, vegetables, legumes and nuts, whole grains and low-fat dairy products), a score ranging from 1 to 5 was attributed to the participants (1 for the

lowest quintile and 5 for the highest quintile). For the components sodium, red and processed meats, and sugar-sweetened beverages the scoring was reversed (5 points for the lowest quintile and 1 for the highest quintile). The component scores were summed up to obtain an overall DASH score ranging from 8 (lowest adherence) to 40 (highest adherence). Subsequently, we divided all patients in tertiles of the overall DASH score.

### 2.5 | Clinical endpoints

The primary outcomes of this study are renal function decline and all-cause mortality. Renal function decline was defined as doubling of serum creatinine and/or death-censored graft failure. Doubling of serum creatinine concentration, defined as the first serum creatinine value that was twice the baseline value, has been used frequently in several clinical nephrology trials to study renal function decline.[24-26] Death-censored graft failure was defined as return to hemodialysis treatment or retransplantation. Data on serum creatinine, death-censored graft failure, and all-cause mortality after baseline were retrieved from patient files until the end of September 2015. Since the outpatient program uses continuous surveillance systems, it guarantees correct and up-to-date information on patient status. No participants were lost to follow-up.

### 2.6 | Statistical analyses

With use of histograms and probability (Q-Q) plots, we tested variable distribution. For descriptive statistics, data are presented as mean and standard deviation when normally distributed, as median and interquartile range when skewed distributed, and as number and percentage in case of categorical data. Differences between the tertiles were compared using 1-way analysis of variance tests for normally distributed, continuous variables, Kruskal-Wallis tests for skewed distributed, continuous variables and $\chi^2$ tests for categorical variables.

We performed multivariable Cox proportional hazards regression analyses to estimate the effect of the DASH diet on renal function decline and all-cause mortality. First we performed analyses adjusted for age and sex (model 1). We further cumulatively adjusted for kidney function parameters (eGFR, proteinuria, time between transplantation and baseline, and primary renal disease) in model 2. We continued with cumulative adjustment for transplant characteristics (acute rejection, pre-emptive transplantation, and donor type) in model 3. Since Cox proportional hazards regression models should not contain more than 10 events per variable,[27] we performed further adjustments for potential confounders in additional models based on model 3. We additionally adjusted for dietary and lifestyle factors (smoking, alcohol consumption, total kcal intake, and physical activity) in model 4; use of immunosuppressive medication (calcineurin inhibitors and prednisolone), trough levels of tacrolimus and cyclosporine, and coefficients of variation (standard deviation/mean × 100%) of calcineurin levels between half a year before baseline to 1 year after baseline in model 5; systolic blood pressure and use of antihypertensive drugs in model 6; BMI in model 7; and low-density lipoprotein (LDL)–cholesterol and total cholesterol in model 8. The DASH score was used as both continuous variable and as categorical variable. Patients were censored at date of last follow-up or death. Hazards ratios and 95% confidence intervals (CIs) were given for the Cox proportional hazards analyses. Schoenfeld residuals of the DASH score were checked and tested in STATA using the proportional hazard test by Grambsch and Therneau.[28] The assumption of proportional hazards was not violated. Penalized splines were constructed to visualize the association of the DASH score on renal function decline and all-cause mortality after adjustment for age and sex.

To study the association of the individual components of the DASH diet and the endpoints, we calculated the median intake of the components in g/d. For all components, we compared an intake above the median with an intake below the median.

In addition, we evaluated potential effect modification by age, sex, systolic blood pressure (SBP), baseline eGFR, smoking status, alcohol consumption, and physical activity. Potential effect modifiers were tested by entering both main effects and the cross-product term in Cox regression analyses. When effect modification was observed, we proceeded with Cox regression analyses in subgroups of RTR stratified by the observed effect modifier. We performed competing risk analyses (as sensitivity analyses) according to Fine and Gray.[29]

All $P$ values were 2-tailed. A $P \leq .05$ was considered statistically significant. All statistical data analyses were performed using IBM Statistics SPSS version 23.0 (IBM Inc., Chicago, IL), STATA version 11.0 (StataCorp LP, College Station, TX), R version 3.2.3 (R Foundation for Statisical Computing, Vienna, Austria), and GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA).

## 3 | RESULTS

### 3.1 | Patient characteristics

Mean age of RTR was 53.0 ± 12.7 years and 56.5% of the participants were men. Median time between baseline and

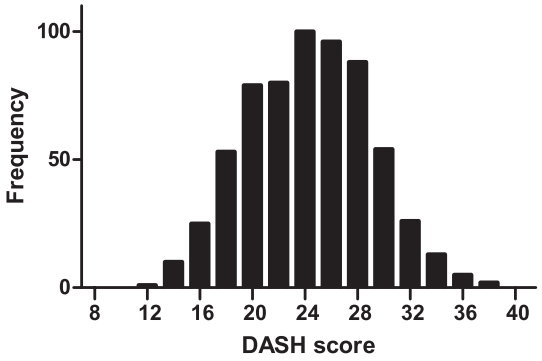


**FIGURE 1** Frequency distribution of the Dietary Approach to Stop Hypertension (DASH) score in the overall renal transplant recipients population (632 participants)

**TABLE 1** Baseline characteristics of the overall RTR population and according to tertiles based on the DASH score

| | Overall RTR | | Tertiles of DASH score | | |
|---|---|---|---|---|---|
| DASH score | 23.8 (n = 632) | 18.5 (n = 206) | 24.0 (n = 238) | 29.3 (n = 188) | *P* |
| Background variables | | | | | |
| Age, y | 53.0 ± 12.7 | 49.5 ± 13.3 | 52.8 ± 12.3 | 57.0 ± 11.3 | <.001 |
| Male sex, n (%) | 357 (56.5) | 146 (70.9) | 126 (52.9) | 85 (45.2) | <.001 |
| Current smokers, n (%) | 77 (12.2) | 39 (18.9) | 22 (9.2) | 16 (8.5) | .001 |
| Alcohol consumption, g/d | 2.6 (0.0-11.1) | 3.8 (0.0-14.7) | 2.5 (0.0-8.7) | 1.6 (0.0-9.7) | .10 |
| Total energy intake, kcal/d | 2175 ± 639 | 2151 ± 667 | 2221 ± 667 | 2144 ± 567 | .38 |
| Physical activity score (time × intensity) | 5245 (2498-8029) | 5460 (1943-8400) | 5050 (2100-8093) | 5280 (2798-7435) | .71 |
| Weight, kg | 80.3 ± 16.5 | 83.4 ± 17.8 | 81.0 ± 16.7 | 76.0 ± 13.9 | <.001 |
| BMI, kg/m$^2$ | 26.6 ± 4.8 | 27.2 ± 5.0 | 27.0 ± 4.8 | 25.6 ± 4.3 | .001 |
| eGFR, mL/min per 1.73 m$^2$ | 52.5 ± 20.1 | 52.7 ± 20.4 | 52.5 ± 20.6 | 52.2 ± 19.3 | .97 |
| Circulation | | | | | |
| Heart rate, bpm | 68.8 ± 12.1 | 67.7 ± 12.1 | 70.2 ± 11.9 | 68.1 ± 12.2 | .07 |
| SBP, mm Hg | 136.2 ± 17.4 | 137.7 ± 18.3 | 137.6 ± 17.7 | 132.7 ± 15.3 | .005 |
| DBP, mm Hg | 82.9 ± 11.0 | 85.2 ± 11.2 | 83.4 ± 11.1 | 79.9 ± 9.8 | <.001 |
| MAP, mm Hg | 100.7 ± 12.0 | 102.7 ± 12.7 | 101.5 ± 12.2 | 97.5 ± 10.4 | <.001 |
| Laboratory parameters | | | | | |
| Triglycerides, mmol/L | 1.7 (1.2-2.3) | 1.7 (1.2-2.6) | 1.8 (1.3-2.2) | 1.5 (1.1-2.1) | .02 |
| Total cholesterol, mmol/L | 5.1 ± 1.1 | 5.2 ± 1.2 | 5.1 ± 1.1 | 5.1 ± 1.1 | .20 |
| HDL-cholesterol, mmol/L | 1.4 ± 0.5 | 1.3 ± 0.4 | 1.4 ± 0.5 | 1.5 ± 0.5 | .03 |
| LDL-cholesterol, mmol/L | 3.0 ± 0.9 | 3.1 ± 1.0 | 3.0 ± 0.9 | 2.9 ± 0.9 | .35 |
| C-reactive protein, mg/dL | 1.6 (0.7-4.5) | 1.8 (0.6-5.0) | 1.6 (0.8-4.5) | 1.5 (0.5-3.8) | .44 |
| Fasting glucose, mmol/L | 5.3 (4.8-6.0) | 5.3 (4.8-6.2) | 5.2 (4.8-6.1) | 5.2 (4.7-5.8) | .43 |
| HbA1C, % | 6.0 ± 0.8 | 6.0 ± 0.8 | 6.0 ± 0.8 | 6.0 ± 0.8 | .91 |
| Urinary parameters | | | | | |
| Sodium excretion, mmol/24 h | 157.2 ± 61.1 | 189.1 ± 66.0 | 153.9 ± 53.0 | 126.5 ± 46.9 | <.001 |
| Potassium excretion, mmol/24 h | 73.2 ± 24.3 | 72.0 ± 24.6 | 71.0 ± 23.6 | 77.2 ± 24.6 | .02 |
| Creatinine excretion, mmol/24 h | 11.7 ± 3.4 | 12.8 ± 3.4 | 11.6 ± 3.5 | 10.4 ± 2.7 | <.001 |
| Urea excretion, mmol/24 h | 391.3 ± 114.7 | 410.4 ± 124.5 | 384.3 ± 111.1 | 379.3 ± 105.5 | .01 |
| Albumin excretion, mg/24 h | 260.9 ± 676.5 | 352.5 ± 826.8 | 256.6 ± 699.8 | 166.7 ± 397.6 | .03 |
| Proteinuria, n (%) | 139 (22.0) | 59 (28.6) | 55 (23.1) | 25 (13.3) | .001 |
| Primary renal disease | | | | | .83 |
| Primary glomerulosclerosis, n (%) | 180 (28.5) | 63 (30.6) | 66 (27.7) | 51 (27.1) | |
| Glomerulonephritis, n (%) | 46 (7.3) | 18 (8.7) | 16 (6.7) | 12 (6.4) | |
| Tubulointerstitial nephritis, n (%) | 74 (11.7) | 27 (13.1) | 25 (10.5) | 22 (11.7) | |
| Polycystic kidney disease, n (%) | 135 (21.4) | 37 (18.0) | 56 (23.5) | 42 (22.3) | |
| Renal hypodysplasia, n (%) | 23 (3.6) | 9 (4.4) | 10 (4.2) | 4 (2.1) | |
| Renovascular diseases, n (%) | 35 (5.5) | 14 (6.8) | 12 (5.0) | 9 (4.8) | |
| Diabetes mellitus, n (%) | 30 (4.7) | 9 (4.4) | 12 (5.0) | 9 (4.8) | |
| Other, n (%) | 109 (17.2) | 29 (14.1) | 41 (17.2) | 39 (20.7) | |
| Transplant characteristics | | | | | |
| Transplant vintage, y | 5.7 (1.9-12.1) | 5.0 (1.7-11.3) | 5.7 (1.9-11.0) | 7.0 (2.1-14.4) | .09 |
| Living donor, n (%) | 216 (34.2) | 71 (34.5) | 81 (34.0) | 64 (34.0) | .99 |

(Continues)

**TABLE 1** (Continued)

| DASH score | Overall RTR | | Tertiles of DASH score | | P |
|---|---|---|---|---|---|
| | 23.8 (n = 632) | 18.5 (n = 206) | 24.0 (n = 238) | 29.3 (n = 188) | |
| Pre-emptive transplant, n (%) | 103 (16.3) | 32 (15.5) | 41 (17.2) | 30 (16.0) | .88 |
| Dialysis duration, mo | 36.0 (20.0-59.0) | 43.0 (13.5-60.0) | 42.0 (30.0-66.0) | 32.0 (16.0-50.0) | .17 |
| Age donor, y | 43.1 ± 15.5 | 42.4 ± 15.7 | 42.5 ± 15.6 | 44.6 ± 15.0 | .29 |
| Cold ischemia time, h | 14.2 (2.6-20.8) | 14.3 (2.7-20.0) | 13.06 (2.60-20.81) | 15.2 (2.6-21.1) | .76 |
| Warm ischemia time, min | 40.0 (33.0-50.0) | 41.0 (33.5-50.0) | 40.0 (33.0-49.5) | 40.0 (33.0-50.0) | .70 |
| Acute rejection, n (%) | 166 (26.3) | 52 (25.2) | 63 (26.5) | 51 (27.1) | .91 |
| Medication | | | | | |
| Calcineurin inhibitor, n (%) | | | | | .36 |
| Cyclosporine | 250 (39.6) | 80 (38.8) | 99 (41.6) | 71 (37.8) | |
| Tacrolimus | 110 (17.4) | 40 (19.4) | 44 (18.5) | 26 (13.8) | |
| Cyclosporine (trough level, μg/L) | 107.0 (77.0-150.0) | 110.0 (77.0-149.0) | 97.5 (75.0-140.3) | 116.0 (77.3-157.8) | .52 |
| Tacrolimus (trough level, μg/L) | 7.1 (5.4-9.1) | 6.7 (5.2-8.4) | 7.7 (6.1-10.9) | 6.6 (4.8-9.4) | .22 |
| CV of CCNI trough levels (%) | 26.6 (17.0-47.0) | 29.1 (18.6-45.0) | 23.9 (17.4-46.7) | 27.0 (14.7-50.0) | .45 |
| Proliferation inhibitor, n (%) | | | | | .29 |
| Azathioprine | 111 (17.6) | 36 (17.5) | 35 (14.7) | 40 (21.3) | |
| Mycophenolate | 418 (66.1) | 132 (64.1) | 162 (68.1) | 124 (66.0) | |
| mTOR inhibitor, n (%) | 10 (1.6) | 4 (1.9) | 2 (0.8) | 4 (2.1) | .52 |
| Prednisolone dose, mg | 10.0 (7.5-10.0) | 10.0 (7.5-10.0) | 10.0 (7.5-10.0) | 10.0 (7.5-10.0) | .27 |
| Diuretics, n (%) | 257 (40.7) | 88 (42.7) | 96 (40.3) | 73 (38.8) | .73 |
| β-Blocker, n (%) | 400 (63.3) | 126 (61.2) | 152 (63.9) | 122 (64.9) | .73 |
| ACE inhibitor, n (%) | 207 (32.8) | 78 (37.9) | 75 (31.5) | 54 (28.7) | .14 |
| Angiotensin II receptor blocker, n (%) | 102 (16.1) | 31 (15.0) | 40 (16.8) | 31 (16.5) | .87 |
| Calcium antagonist, n (%) | 156 (24.7) | 60 (29.1) | 59 (24.8) | 37 (19.7) | .09 |
| Statins, n (%) | 336 (53.2) | 106 (51.5) | 121 (50.8) | 109 (58.0) | .23 |

ACE, angiotensin-converting enzyme; BMI, body mass index; bpm, beats per minute; CV, coefficient of variation, CCNI, combined calcineurin inhibitor; DASH, Dietary Approach to Stop Hypertension; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure; mTOR, mammalian target of rapamycin; RTR, renal transplant recipients; SBP, systolic blood pressure.

Data are represented as mean ± SD, median (interquartile range), or n (%). Differences were tested by analysis of variance or Kruskal-Wallis for continuous variables and with $\chi^2$ test for categorical variables.

transplantation was 5.7 (interquartile range [IQR], 1.9-12.1) years. The DASH score varied between 12 (lowest adherence) and 37 (highest adherence), with a mean score of 23.8 ± 4.7 (Figure 1). Baseline characteristics of the overall RTR population and according to tertiles based on the sex-specific DASH score are shown in Table 1. RTR with a high adherence to the DASH diet were older, more often female, more frequently nonsmokers, and had a lower BMI compared to patients with a low adherence to the DASH diet. Furthermore, RTR with a high DASH score had a lower blood pressure, lower fasting triglycerides, and higher high-density lipoprotein (HDL)–cholesterol concentrations. Moreover, RTR in the tertile with the highest DASH score had lower 24-hour urinary sodium, higher 24-hour potassium, and lower 24-hour urea excretion levels, and less proteinuria when compared to RTR in the tertile with the lowest DASH score.

## 3.2 | DASH score and renal function decline

During median follow-up of 5.3 (IQR, 4.1-6.0) years, 119 (18.8%) RTR had renal function decline. Cox regression analyses with the DASH score analyzed as continuous variable showed that a higher DASH score was associated with a lower risk of renal function decline (hazard ratio [HR] = 0.95; 95% CI, 0.91-0.99, *P* = .008), when adjusted for age and sex (Table 2). Adjustment for other potential confounders, including kidney function parameters, transplant characteristics, and dietary and lifestyle factors, did not materially change the association. We proceeded with multivariable Cox proportional hazards models for analyses of tertiles of the DASH score. RTR in the highest tertile had >50% lower risk of renal function decline (HR = 0.46, 95% CI, 0.28-0.76, *P* = .002) when compared to the lowest tertile, independent of age and sex.

**TABLE 2** Association of the DASH score with renal function decline and all-cause mortality

| | DASH score as continuous variable | | Tertiles of DASH score | | | | |
|---|---|---|---|---|---|---|---|
| | | | T1 | T2 | | T3 | |
| | HR (95% CI) | *P* value | Reference | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Renal function decline | | | | | | | |
| No. of events | 119 | | 53 | 42 | | 24 | |
| Model 1 | 0.95 (0.91-0.99) | .008 | 1.00 | 0.65 (0.43-0.98) | .04 | 0.46 (0.28-0.76) | .002 |
| Model 2 | 0.95 (0.91-0.99) | .03 | 1.00 | 0.67 (0.44-1.02) | .06 | 0.54 (0.32-0.91) | .02 |
| Model 3 | 0.96 (0.92-1.00) | .08 | 1.00 | 0.72 (0.47-1.10) | .13 | 0.57 (0.33-0.96) | .03 |
| Model 4 | 0.96 (0.91-1.00) | .05 | 1.00 | 0.70 (0.45-1.10) | .12 | 0.57 (0.33-0.97) | .04 |
| Model 5 | 0.96 (0.92-1.00) | .08 | 1.00 | 0.75 (0.48-1.16) | .19 | 0.56 (0.33-0.95) | .03 |
| Model 6 | 0.96 (0.91-1.00) | .05 | 1.00 | 0.72 (0.47-1.10) | .13 | 0.54 (0.32-0.93) | .03 |
| Model 7 | 0.96 (0.91-1.00) | .05 | 1.00 | 0.70 (0.46-1.07) | .10 | 0.53 (0.31-0.91) | .02 |
| Model 8 | 0.95 (0.91-0.99) | .03 | 1.00 | 0.66 (0.42-1.01) | .06 | 0.52 (0.30-0.88) | .02 |
| All-cause mortality | | | | | | | |
| No. of events | 128 | | 47 | 48 | | 33 | |
| Model 1 | 0.95 (0.91-0.99) | .01 | 1.00 | 0.68 (0.45-1.03) | .07 | 0.48 (0.30-0.77) | .002 |
| Model 2 | 0.95 (0.91-0.99) | .01 | 1.00 | 0.68 (0.45-1.04) | .07 | 0.50 (0.31-0.80) | .004 |
| Model 3 | 0.95 (0.92-0.99) | .02 | 1.00 | 0.70 (0.46-1.05) | .09 | 0.52 (0.32-0.83) | .006 |
| Model 4 | 0.96 (0.92-1.00) | .03 | 1.00 | 0.71 (0.45-1.10) | .13 | 0.53 (0.32-0.86) | .01 |
| Model 5 | 0.96 (0.92-0.99) | .03 | 1.00 | 0.70 (0.46-1.08) | .11 | 0.51 (0.31-0.82) | .005 |
| Model 6 | 0.95 (0.91-0.99) | .01 | 1.00 | 0.70 (0.46-1.07) | .10 | 0.49 (0.30-0.79) | .003 |
| Model 7 | 0.95 (0.91-0.99) | .02 | 1.00 | 0.70 (0.46 -1.06) | .09 | 0.49 (0.30-0.79) | .004 |
| Model 8 | 0.94 (0.90-0.98) | .005 | 1.00 | 0.59 (0.39-0.91) | .02 | 0.47 (0.29-0.75) | .002 |

BMI, body mass index; DASH, Dietary Approach to Stop Hypertension; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Cox proportional hazards regression analyses was performed to assess the association of the DASH score on renal function decline and all-cause mortality. Mean DASH scores were as follows: T1: 18.5, T2: 24.0, and T3: 29.3.

- Model 1, adjustment for age and sex
- Model 2, model 1+ adjustment for kidney function parameters (eGFR, urinary protein excretion, time between transplantation and baseline and primary renal disease)
- Model 3, model 2+ adjustment for transplant characteristics (acute rejection, pre-emptive transplantation, donor type)
- Model 4, model 3+ adjustment for dietary and lifestyle factors (smoking, alcohol consumption, total kcal intake, and physical activity)
- Model 5, model 3+ adjustment for use of immunosuppressive medication (calcineurin inhibitors, prednisolone), trough levels of both tacrolimus and cyclosporine, and coefficients of variation of calcineurin inhibitors trough levels
- Model 6, model 3+ adjustment for SBP + use of antihypertensive drugs
- Model 7, model 3+ adjustment for BMI
- Model 8, model 3+ adjustment for LDL-cholesterol + total cholesterol.

After adjustment for kidney function parameters and transplant characteristics, the association remained significant (HR = 0.57; 95% CI, 0.33-0.96, *P* = .03). The association remained materially unchanged after further adjustment for other potential confounders (Table 2, models 4-7). To illustrate the association of the DASH score and renal function decline, an age- and sex-adjusted penalized spline is shown in Figure 2.

### 3.3 | DASH score and all-cause mortality

We continued with analyses for the association of the DASH score on all-cause mortality. During follow-up, 128 (20.3%) died. Cox regression analyses with the DASH score analyzed as continuous variable showed that a higher DASH score was associated with a lower risk of all-cause mortality (HR = 0.95; 95% CI, 0.91-0.99, *P* = .01), when adjusted for age and sex (Table 2). Adjustment for other potential confounders did not materially change the association. We proceeded with multivariable Cox proportional hazards models for analyses of tertiles of the DASH score. RTR in the highest tertile had >50% lower risk of all-cause mortality (HR = 0.48, 95% CI, 0.30-0.77, *P* = .002) when compared to the lowest tertile, independent of age and sex. Adjustment for other potential confounders, including kidney function parameters and transplant characteristics, did not materially change the results (HR = 0.52; 95% CI, 0.32-0.83, *P* = .006). The association remained materially unchanged after

further adjustment for other potential confounders (Table 2, models 4-7). To illustrate the association of the DASH score and all-cause mortality, an age- and sex-adjusted penalized spline is shown in Figure 2.

### 3.4 | Individual components of the DASH score

The association of the individual components of the DASH score on renal function decline and all-cause mortality, adjusted for age, sex, kidney function parameters, and transplant characteristics are shown in Table 3. A higher intake of fruit was associated with a lower risk of renal function decline (HR = 0.65; 95% CI, 0.44-0.95, $P$ = .03) and all-cause mortality (HR = 0.68; 95% CI, 0.48-0.98, $P$ = .04). Furthermore, a higher intake of sugar-sweetened beverages was associated with an increased risk of all-cause mortality (HR = 1.52; 95% CI, 1.06-2.19, $P$ = .02), but not with renal function decline.

### 3.5 | Effect modifications

We observed that the association of the DASH score with renal function decline was modified by baseline eGFR ($P_{interaction}$ = .005) and smoking behavior ($P_{interaction}$ = .01), independent of age and sex (Figure 3). The association of the DASH score with all-cause mortality was only modified by baseline eGFR ($P_{interaction}$ = .002), independent of age and sex (Figure 4). No further evidence was found for effect modification by sex, SBP, smoking behavior, alcohol consumption, and physical activity ($P_{interaction}$ ≥ .05). Higher adherence to the DASH score was associated with a lower risk of renal function decline and all-cause mortality in the subgroup of RTR with higher eGFR (eGFR≥45 mL/min per 1.73 $m^2$), but not in the subgroup of RTR with lower eGFR (eGFR<45 mL/min per 1.73 $m^2$). Furthermore, higher adherence to the DASH score was associated with a lower risk of renal function decline in smokers, but not in nonsmokers.

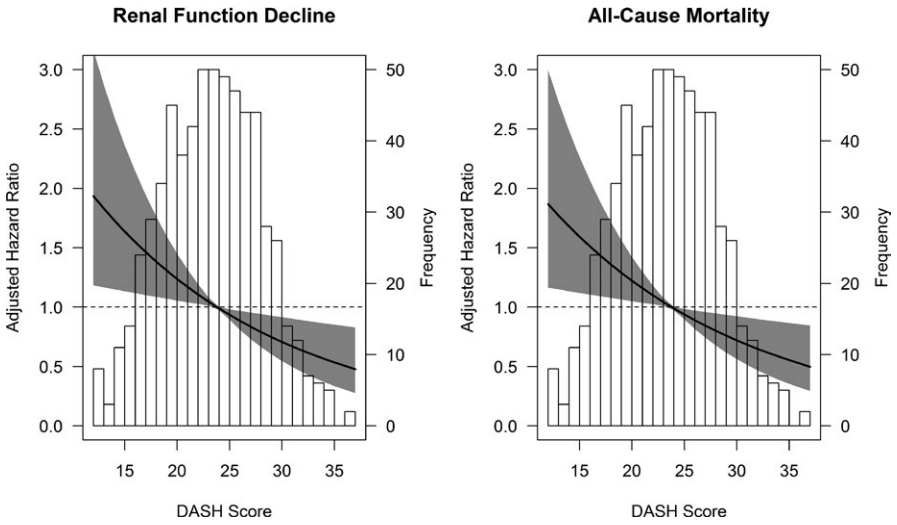


**FIGURE 2** Association between the Dietary Approach to Stop Hypertension (DASH) score on renal function decline and all-cause mortality in 632 renal transplant recipients. Data were fit by a Cox regression model based on penalized splines and adjusted for age and sex. The gray area represents the 95% confidence interval

**TABLE 3** Association per component of the DASH diet with renal function decline and all-cause mortality

| | | Renal function decline | | All-cause mortality | |
|---|---|---|---|---|---|
| Components | Median (g/d) | Low intake Reference | High intake HR (95% CI) | Low intake Reference | High intake HR (95% CI) |
| Fruits | 123.00 | 1.00 | 0.65 (0.44-0.95) | 1.00 | 0.68 (0.48-0.98) |
| Vegetables | 80.06 | 1.00 | 0.77 (0.53-1.13) | 1.00 | 0.87 (0.61-1.24) |
| Legumes and nuts | 36.93 | 1.00 | 0.75 (0.51-1.09) | 1.00 | 0.93 (0.65-1.33) |
| Whole grains | 102.00 | 1.00 | 0.77 (0.53-1.14) | 1.00 | 0.75 (0.52-1.09) |
| Low-fat dairy products | 232.86 | 1.00 | 1.06 (0.74-1.54) | 1.00 | 0.74 (0.52-1.06) |
| Sodium | 3.40 | 1.00 | 0.94 (0.63-1.40) | 1.00 | 0.76 (0.52-1.11) |
| Red processed meat | 67.98 | 1.00 | 1.02 (0.71-1.48) | 1.00 | 0.81 (0.57-1.16) |
| SSB | 154.47 | 1.00 | 0.97 (0.66-1.42) | 1.00 | 1.52 (1.06-2.19) |

CI, confidence interval; DASH, Dietary Approach to Stop Hypertension; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RTR, renal transplant recipients; SSB, sugar-sweetened beverages.

Cox proportional hazards regression analyses was performed to assess the association per component of the DASH score with renal function decline and all-cause mortality. For all components, the RTR with intake > median are compared to RTR with intake < median. Adjusted for age, sex, kidney function parameters (eGFR, urinary protein excretion, time between transplantation, and baseline and primary renal disease), and transplant characteristics (acute rejection, pre-emptive transplantation, and donor type).

### 3.6 | Sensitivity analyses

The results of competing risk analyses did not materially differ from those with Cox regression, with, for example, a HR of 0.48 (95% CI, 0.29-0.79) for the association of the highest tertile of DASH score with renal function decline compared to the lowest tertile in model 1 with adjustment for age and sex (Table 2 for comparison) and a HR of 0.59 (95% CI, 0.35-0.99) in model 3 with adjustment for age, sex, kidney function parameters, and transplant characteristics (Table 2 for comparison).

## 4 | DISCUSSION

This study showed that high adherence to a DASH-style diet was associated with a lower risk of renal function decline and all-cause mortality in RTR. In addition, these associations were modified by baseline eGFR, and for the association with renal function decline also by smoking behavior.

The results of our study are consistent with previous findings on the beneficial effect of a DASH-style diet on renal function and patient survival. High adherence to the DASH diet was associated with a 45% reduction in the risk of a rapid decline in eGFR in older white women.[30] Moreover, in a cross-sectional study among the urban poor in the United States, low adherence to the DASH diet was associated with a higher risk of chronic kidney disease (CKD).[31] A recent prospective study showed that high adherence to the DASH diet was inversely associated with prevalence of CKD in an Iranian population.[32] Not only is the DASH diet associated with a lower risk of renal failure in the general population, but also high adherence to the DASH diet is associated with lower mortality rates in women with heart failure[33] and adults with hypertension.[34] To the best of our knowledge, the DASH diet has not previously been studied in RTR.

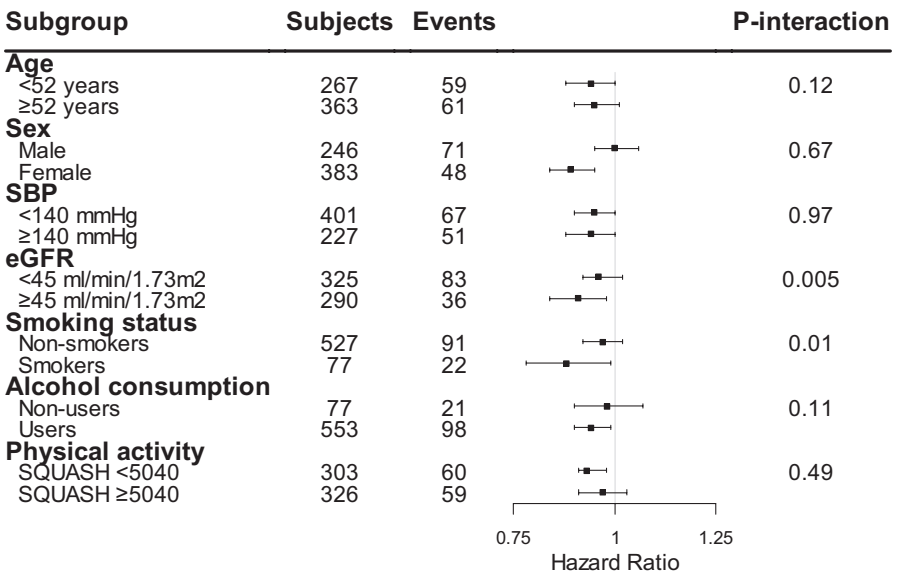


**FIGURE 3** Stratified analyses of the association of the DASH score on renal function decline in RTR adjusted for age and sex. Subgroups with $P < .05$ were considered effect modifiers. BMI, body mass index; DASH, Dietary Approach to Stop Hypertension; eGFR, estimated glomerular filtration rate; RTR, renal transplant recipients; SBP, systolic blood pressure; SQUASH, Short QUestionnaire to ASsess Health enhancing physical activity

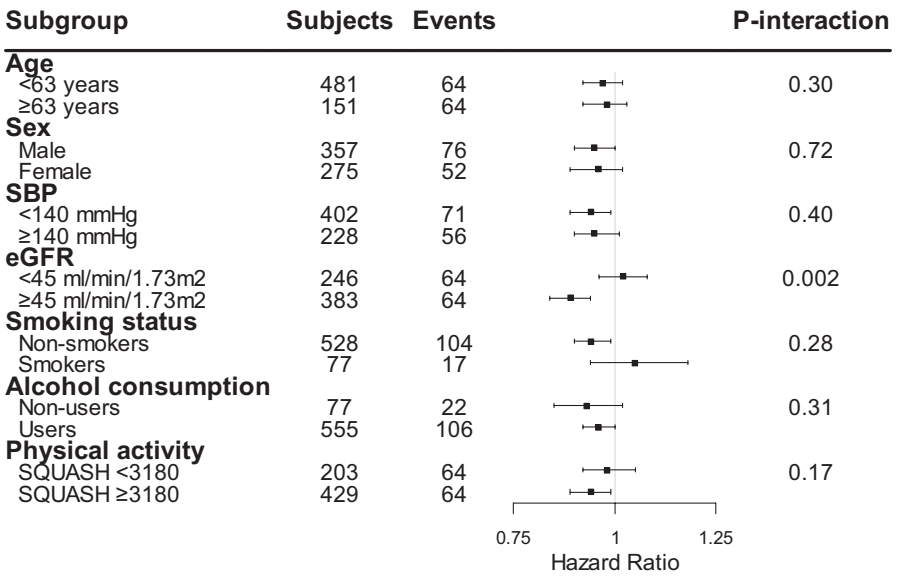


**FIGURE 4** Stratified analyses of the association of the DASH score on all-cause mortality in RTR adjusted for age and sex. Subgroups with $P < .05$ were considered effect modifiers. BMI, body mass index; DASH, Dietary Approach to Stop Hypertension; eGFR, estimated glomerular filtration rate; RTR, renal transplant recipients; SBP, systolic blood pressure; SQUASH, Short QUestionnaire to ASsess Health enhancing physical activity

The DASH diet consists of a high intake of fruit, vegetables, whole grains, low-fat dairy products, legumes and nuts, and a low intake of sodium, sugar-sweetened beverages, and red processed meat.[10,11] This study showed that the beneficial effect of the total DASH score is stronger than the individual components of the DASH diet alone. We found that a high intake of fruit was associated with a lower risk of renal function decline and all-cause mortality when compared to a low intake of fruit. Previous prospective cohort-studies showed that high intake of fruits, vegetables, and whole grains is inversely associated with kidney function decline[30] and all-cause mortality in the general population.[35,36] For the consumption of fruit, this is in agreement with our study, but not for the intake of vegetables and whole grains. Furthermore, we found that a high intake of sugar-sweetened beverages was associated with a higher risk of all-cause mortality, which is in line with previous literature.[37]

We found that there was a significant association between the DASH diet and both renal function decline and all-cause mortality in the subgroup of RTR with a higher baseline eGFR. It is known that a decline in kidney function is associated with a progressive increase in cardiovascular risk.[38] In addition, in patients with impaired renal function, cardiovascular risk factors, including hypertension, diabetes, albuminuria, anemia, vascular stiffness, metabolic acidosis, and dyslipidemia are common.[38,39] Moreover, these patients often deal with multimorbidity[40]; hence, they may not be able to benefit enough from only high adherence to the DASH diet. In our study, we also found a significant association of the DASH diet with decline of renal function in smokers and not in nonsmokers. However, the reliability of this finding is doubtful, since the number of smokers in this RTR population is relatively small. It is known that smoking after renal transplantation is a risk factor for both graft failure and all-cause mortality in RTR; however, past smoking is only a risk factor for all-cause mortality, but not for graft failure.[41] Furthermore, smoking in living kidney donors is associated with reduced patient survival, but not with graft survival.[42] Unfortunately, we could not take into account changes in smoking status beyond baseline and information on smoking status of RTR and donors before transplantation, since these data were not available.

It is known that the DASH diet effectively lowers blood pressure.[43] In line with this, we found significant cross-sectional inverse associations of DASH score with systolic blood pressure, diastolic blood pressure, and mean arterial pressure. However, the association of the DASH score with both endpoints remained significant after adjustment for baseline data on systolic blood pressure and use of antihypertensive drugs. Although the prospective associations of DASH score with long-term outcomes were independent of baseline blood pressure, we do not know if subjects with higher DASH scores continued to have better-controlled blood pressure over time, which leaves the possibility that the beneficial effects of the DASH diet are mediated by blood pressure. Previous studies showed that the DASH diet improves the lipid profile by lowering triglyceride levels, total cholesterol, and LDL-cholesterol concentration.[44-46] In the baseline characteristics of this study, we observe lower triglyceride levels and higher HDL concentrations in the highest tertile of the DASH score compared to the lowest tertile. No differences in LDL-cholesterol and total cholesterol concentrations were found. After adjustment for total cholesterol and LDL-cholesterol, the association of the DASH score and all primary and secondary endpoints became stronger, again suggesting multiple mechanisms behind the beneficial effect of the DASH diet. Additionally, the DASH diet affects inflammation, since this dietary pattern reduces circulating C-reactive protein (CRP) concentrations.[47,48] However, the DASH diet did not affect other inflammatory biomarkers, such as tumor necrosis factor-α, interleukin-6, and adiponectin.[47,48] Nevertheless, in our study we observed no difference in CRP concentrations between the tertiles. Recently, a prospective study showed that posttransplant CRP concentrations are inversely associated with graft function after renal transplantation.[49] This has also been noted in a prospective study, which concluded that high serum CRP concentrations were associated with impaired renal function and a higher risk of graft failure in RTR compared to low and intermittent serum CRP concentrations.[50] Another mechanism could be the antioxidant properties of several components of the DASH diet, such as fruits, vegetables, and whole grains, which are rich in phytochemicals.[51]

Strengths of this study include the use of a reproducible and biomarker validated FFQ, and the availability of 24-hour urinary sodium excretion to assess salt intake. Since salt intake varies widely in both processed and home-cooked meals, it is difficult to quantify sodium intake using a FFQ.[23] Another strength of the current study is the complete follow-up. Furthermore, the clinical endpoints—decline of renal function and all-cause mortality—are very relevant in daily practice. There are also several limitations. First, this prospective cohort study is a single-center study, with a study population that consisted mainly of white people. Therefore, it is unclear whether our findings can be extrapolated to other populations. It would be relevant to repeat our study in other patient populations. Furthermore, information on dietary intake was assessed at a single time point at baseline, which may not be an accurate reflection of diet longitudinally. It should, however, be noted that most epidemiological studies use single baseline measurements to investigate associations with long-term outcomes, which is likely to adversely affect strengths of these associations with outcome and therefore likely leads to underestimation of associations between baseline measurements and long-term outcome rather than overestimation.[52,53]

In conclusion, this single-center study of stable RTR showed that high adherence to a DASH-style diet is associated with a lower risk of both renal function decline and all-cause mortality. This study adds to the current evidence that a healthful dietary pattern, such as the DASH diet, could offer an approach to prevent renal function decline and all-cause mortality after renal transplantation. However, our study is observational in nature, and therefore a randomized clinical trial is required to actually demonstrate that adherence to the DASH diet positively affects long-term outcomes in renal transplant recipients.

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## AUTHOR CONTRIBUTIONS

EvdB, GJN, and SJLB: designed and conducted the research; MCJO and AWG-N: analyzed the data and performed statistical analysis; MCJO, AWG-N, and SJLB wrote the manuscript; AWG-N, EC, ROBG, MHdB, EvdB, SSS-M, DK, GJN, and SJLB contributed to the interpretation of the results and provided important advice and intellectual content; MCJO and SJLB had primary responsibility for final content. All authors read and approved the final manuscript.

## DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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